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In venturing to address you this evening on the subject of uræmic intoxications, I am not unmindful of the difficulties that are inseparable from the problem which I shall undertake to discuss. Indeed it cannot be denied that one of the attractions of this subject is the obscurity which surrounds the oft-recurring phenomena which we call uræmic—phenomena that have excited the interest and baffled the insight of Richard Bright, of Traube, of Frerichs, and of many lesser intellects.

Although a study of uræmia that has extended over many years does not make it possible for me to isolate, as definitely as could be wished, the pathological factors concerned in the production of the symptoms of uræmia, I believe I can, at least, indicate the direction in which we should look for an explanation of the nature of these symptoms. It will be my purpose to show that the clinical phenomena which we include under the term uræmia are dependent on toxæmic states rather than upon primarily mechanical causes. In doing this I shall make use of observations which I have accumulated from the study of the blood in 28 cases of uræmia, which have either been observed by me in my medical service in the City Hospital, or have been placed at my disposal by interested colleagues. In addition to this, I shall draw upon facts which have come to my knowledge from a study of experimental uræmic states. It would be a satisfaction to present these facts in full detail, but as this could hardly be done without exhausting your patience, a summary of results must suffice for the present

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purpose.[1] For the sake of convenience, the facts to be surveyed may be grouped under the following subjects : the toxic properties of the blood in uræmic states as measured by intravenous infusion ; the relation of uræmia to the urea of the blood, to the extractive substances, and to the potassium salts ; cerebral œdema and uræmia ; the internal secretion of the kidney and uræmia ; experimental uræmia from double nephrectomy and its relation to human obstructive uræmia, and other types of human uræmia.

A question of fundamental importance in the pathology of uræmia is whether the blood in this condition is more toxic when introduced into the circulation of animals than is human blood from normal persons. In the hope of answering this question, the blood serum from 28 uræmic patients, who were bled during life, was introduced intravenously into rabbits, proper precautions being taken as regards the freshness of the serum, its temperature, the rate of infusion, the exclusion of air from the vein, etc. The observations were not confined to rabbits, but included in some instances dogs and monkeys. Two different methods of intravenous infusion were employed. In one case the serum was infused into the femoral vein at a fixed rate until the commencement of fatal symptoms. In the other case, the serum was injected in much smaller amount, either into the femoral vein or into an ear vein with a view to ascertaining the minimum dose capable of causing death in the course of 24 or 36 hours. A difficulty which at once confronts the investigator in the use of these methods is the fact that normal human serum is in itself toxic to rabbits in a considerable degree, owing chiefly perhaps to its power of inducing coagulation. Thus I have found that its requires from 25—40 c.c. of normal human serum to the kilo to initiate fatal symptoms in rabbits when the method of continuous infusion is employed, while it seems generally agreed among investigators that the fatal dose of human serum, as employed by the second method, is from 9—12 c c. per kilo. Inasmuch as it is found that there is considerable variation in the toxicity of the same serum for different rabbits of the same weight, notwithstanding every precaution in making the infusion, it is clear that it is necessary to observe much care in concluding that a given class of serums is more than normally toxic.[2]

Of the uræmic serums which were studied with respect to their

[1] The details of the experimental observations will be elsewhere published.

[2] Uhlenhuth claims that the serum should be subcutaneously injected into guinea pigs to avoid the error incidental to intravenous infusions. In several instances where I have employed this method, there seems to be no doubt that the blood was more than normally toxic, judging from the standard of normal toxicity given by Uhlenhuth.

toxicity, 19 were obtained from cases of uræmia characterized by the occurrence of well marked and repeated convulsive seizures,[1] six of these being instances of puerperal eclampsia. In the nine remaining cases the serum was obtained from patients with chronic nephritis, characterized by dyspnœa and high tension pulse—none of these patients having had convulsive seizures. The inferences which we may make from the study of these serums are as follows : The cases of nephritis characterized by dyspnœa and high tension pulse without convulsions, taken as a class, do not yield positive indications that the toxicity of the serum was greater than normal, although in at least two of the nine cases the toxicity was considerably greater than any I have observed in health. On the other hand the least toxic of these serums possess toxic values that come so near the highest toxic values observed in normal serums that we cannot be certain that they are quite normal. More observations are required before a final judgment can be formed regarding these cases. Taken as a class, the serums from the convulsive group of uræmias show a degree of toxicity distinctly greater than any which I have observed for normal serums, and although there are a few of the 19 cases in which the results are difficult to interpret, there seems to be no doubt that an increase in the toxic properties of the blood is a characteristic of cases of convulsive uræmia. This latter statement apparently holds good also of certain serums from patients with puerperal eclampsia, but here again more observations are required. Volhardt has quite recently denied that there is any increase in the toxic properties of the blood of eclamptic patients, but his results cannot be regarded as final.

Admitting that the serum in convulsive uræmia is more toxic than normal serum, the question at once arises, what is the cause of this pathological increase ?

It is not possible at present to give a satisfactory answer to this question, but the following facts bear upon it. In the first place the toxicity of uræmic serum for animals is greatly reduced by exposure to moderate heat, say 60°C. for a few minutes. This is also true of the toxic properties of normal human serum. These facts suggest that the increased toxicity of uræmic blood is dependent on the presence of an increased amount of a toxic proteid substance which is normally present in the blood.[2] We cannot, however, feel certain that the increased toxicity of the serum does not depend on some

[1] In one of these cases there were merely coarse twitchings never amounting to typical convulsions.

[2] The toxic properties of urea, extractives, salts, etc., are of course not influenced by so moderate an elevation of temperature.

unknown foreign substance. A fact which strengthens the view that a proteid substance is responsible for the toxicity of uræmic, as of normal serum, is that the removal of the proteids by means of absolute alcohol almost wholly deprives the serum of toxic properties.

In trying to form an estimate of the significance of an increase in the toxic properties of uræmic as contrasted with normal serums, it is important to recognize that such an increase in toxicity does not constitute proof that the cause of this augmented toxicity is the cause of the obtrusive cerebral symptoms of uræmia. It is conceivable that alterations may occur in the blood which possess little pathological significance for the human organism, but which are nevertheloss capable of rendering the serum more toxic than normal when introduced into the circulation of rabbits This does not, however, seem a probable explanation of the phenomenon of augmented serum toxicity, and is especially at variance with the fact that our uræmic serums have, in some instances, exhibited very striking toxic properties when introduced into dogs and monkeys, which do not possess the peculiar susceptibility to normal human serum that is observed in the case of rabbits. It is much more rational to regard the increase in the toxic properties of the blood in certain, if not in all, cases of uræmia as evidence of a toxæmia, which is in some way connected with the symptoms of the uræmic state. It is possible that this toxæmia is distinctive of uræmia and always of the same character, but there are certain differences in the behaviour of different serums which make it likely that the toxæmia is not always the same. It is, moreover, certain that the toxic properties of the blood are augmented in conditions not uræmic in nature, for example, in acute lobar pneumonia, in scarlet fever, etc.

Urea being by far the largest and most important constituent of the urine and representing the terminal product of proteid metabolism, it is not singular that this substance should have been for a long time regarded as the main factor in the production of uræmia. It is thus of the highest importance to determine the actual relation of urea to uræmic states. The conclusions reached by me in reference to this relation are based upon a considerable number of determinations of urea in the blood of uræmic persons, of persons with other pathological conditions than uræmia, and of entirely normal persons. Many of these observations were made upon blood drawn during life, but these were supplemented by others upon post-mortem blood, after it was demonstrated both in man and in animals that the urea content of ante- and post-mortem blood corresponds closely in the case of blood taken from well preserved bodies. In addition to making seventy

observations on the urea of human blood, an endeavour was made to determine to what extent chemically pure urea possesses toxic properties. The results of these studies may be briefly stated as follows:

(*a*) In a small proportion of typical cases of uræmia, characterized by the occurrence of convulsions, the urea content of the blood was found to be well within the normal limits, notwithstanding that in these same cases the blood serum was distinctly more toxic than normal. It is plain that in these cases there is no ground for looking with suspicion upon urea as a factor in producing symptoms.

(*b*) In the majority of cases of uræmia, especially in those cases in which the secretion of urine has for a long time been scanty, the urea of the blood was distinctly increased, this increase sometimes reaching to 5 or 10 or even 20 times the normal urea content. It is, however, a very striking fact that many cases of chronic nephritis were found to be characterized by a markedly excessive urea content, even where there were no symptoms that would ordinarily be called uræmic. This is merely a confirmation of an old observation by Bright and Christison which has not received the attention which it deserves. Among the cases in which the urea was increased in the absence of typical uræmic symptoms were 14 cases of acute lobar pneumonia with fatal termination. These cases make it clear that renal inadequacy is a feature of many fatal pneumonias. Whether such inadequacy is to be considered uræmic in the absence of the usual symptoms of uræmia will be considered later.

(*c*) Experimental studies upon dogs and monkeys show that pure urea is toxic when infused intravenously, but only when very large quantities are employed, *i.e.*, quantities equal to many times the daily urea excretion of the animal. The symptoms produced by such infusions are fairly constant in dogs, and consist in initial slower and stronger heart action, copious diuresis, diarrhœa, contraction of the pupils, irregular fibrillary contractions of the muscles, and finally general and severe tonic or clonic spasms and death. If we make the bold assumption that in human nephritis the susceptibility of the nervous system to the influence of urea is similar to that observed in dogs, we would expect convulsive seizures to arise in man when the urea content of the blood reaches about .5 per cent. It was found however, that in many of the cases of human nephritis, in which convulsions occurred, the percentage of urea was considerably below this point, while in a few cases in which this percentage was much exceeded, convulsions were absent.

It is, of course, obvious from the foregoing facts that urea does not play a necessary part in the causation of the symptoms of human

convulsive uræmia. This does not, however, prove that the accumulation of the urea in the blood in large excess is of little importance. There is good evidence that such an accumulation points to a considerable degree of degeneration of the secreting epithelium, and the degeneration which permits the storage of urea, permits the storage of other constituents of the blood, including sodium chloride, potassium salts, nitrogenous extractives, and possibly a toxic proteid substance. It is partly on account of this multiplicity of substances retained in the blood at the same time with urea that we are unable to fix more definitely on the part which urea plays as a toxic substance. It is on the whole very likely that urea in conjunction with the accumulation of other substances in the blood, as the result of renal insufficiency, exerts an influence in the production of uræmic symptoms—especially uræmic vomiting and diarrhœa. The urea of the blood has been greatly increased in all the instances of uræmic vomiting and diarrhœa that I have had an opportunity to study.

It is desirable to indicate here that the customary determination of urea in the urine in cases of nephritis gives no more indication of the quantity of urea in the blood than does a mere record of the volume and specific gravity of the urine passed by such patients, and that it is hence an unnecessary procedure. If the kidneys are incompetent a large reduction in the urea excreted is indicated sufficiently by the reduction in the total solids, this being expressed by the volume and specific gravity. If there is only a moderate daily reduction in the urea excretion this cannot be discovered by the ordinary methods used. To determine this it would be necessary to keep a daily record of the nitrogen taken into the body, of the nitrogen of the urine and of the fæces, and also of the body weight. It is easy to see how, in the course of a few months of mild renal incompetency, the urea of the blood would increase enormously if the kidney lagged only to the extent of a few grams of urea daily—too small an amount to miss by ordinary examinations. It is no exaggeration to state that for practical purposes the consideration of the volume and specific gravity of the urine yields all the information that can be obtained by determining the urea of the urine. What we really require is an estimate of the urea of the blood in our nephritic patients, and this is entirely practicable, for only a few cubic centimetres of blood are necessary for this purpose. I have no doubt that this procedure will in time be frequently employed, as the urea content of the blood is a most important indication of the competency or incompetency of the kidneys.

In recent years there has been some disposition to regard the

extractive substances as the cause of uræmic symptoms, but the evidence in support of this view has never been strong. The results of a personal study of this question may be briefly referred to. The extractives of the blood, that is, the substances which can be extracted by means of ether and alcohol, were determined in more than one hundred instances, including normal human and dog's blood, blood from nephritis with and without uræmic symptoms, from septicæmia, acute lobar pneumonia, etc. It was found that there is no definite relation between uræmia and the quantity of extractives in the blood.

In general the extractives are somewhat increased where the quantity of urea is increased, but there are cases of uræmia where the extractives are apparently normal in amount, and there are cases which would not usually be classed as uræmic where the extractives are markedly increased. The evidence indicates that while extractive substances in excess cannot be regarded as entirely harmless for the organism, they certainly cannot be looked upon as playing other than an auxiliary part in the production of uræmic symptoms. In this connection it may be stated that Dr. A. J. Wakeman, at my request, made a series of laborious observations on the blood of uræmic patients with the use of the Otto-Stas method, for the purpose of isolating any alkaloidal substances which might exist there. The injection into guinea pigs of the material recovered by the Otto-Stas method yielded wholly negative results.

The conclusions that have been stated regarding the extractives of the blood are applicable to the potassium salts theory of uræmia, which was originally advanced by Felz and Ritter, and which constitutes a most instructive chapter in the history of theories of uræmia. Numerous observations made by me confirm the statement of Horbaczewski that the content of potassium salts in uræmic blood may be quite normal in amount. This seems to be especially true of the blood of puerperal eclampsia. These salts are, however, distinctly increased in many instances of uræmia, but apparently never enough to make them wholly responsible for grave nervous symptoms. The potassium theory as an *exclusive* cause of uræmia has recently been revived in France by Charrier, but upon wholly insufficient grounds. It may be said at present that, while the potassium salts cannot be considered to play a leading part in the production of uræmic symptoms, their presence in excess in the blood must be regarded as a possible factor in precipitating symptoms of intoxication.

The ammonium carbonate theory of Frerichs, once so popular, has now only a historical interest and need not be discussed here. An allied hypothesis has, however, been suggested, namely, that the cause

of uræmia is the presence in the blood of the ammonium salt of carbamic acid—ammonium carbamate. The recent investigations of Hahn Pawlow, Massen and Nencki render it probable that urea is formed in the liver by the dehydration of ammonium carbonate, and this fact has led some physiologists to suspect that the highly toxic ammonium carbamate may be responsible for uræmic states. This view appears to me to be at variance with the following facts:

1. In watery solution ammonium carbamate is very unstable and is rapidly converted into ammonium carbonate. We know, however, that ammonium carbonate does not occur in uræmic blood in sufficient amount to produce symptoms, and usually cannot be found at all.

2. The toxicity of uræmic blood is not lessened by dialysis, as it would be if the toxicity depended on a diffusible ammonium salt; nor does the diffusate contain ammonium.

3. The urine of uræmic patients does not necessarily contain an increased proportion of N. of ammonia, as it should do if the synthesis of urea were impaired. On the other hand, in liver diseases in which there is extensive parenchymatous destruction, the N. of ammonia may be greatly increased, even in the absence of uræmic symptoms.

Owing to the instability of ammonium carbamate its isolation from the blood is impracticable, and inferences as to its occurrence there depend chiefly on indirect evidence. The conclusion seems justified that such knowledge as we possess does not support the supposition that ammonium carbamate is concerned with the production of uræmic intoxications.

Before passing to the more constructive consideration of the uræmic problem, it is proper to make brief reference to two widely different theories of the nature of uræmia. One of these is the celebrated hypothesis of Traube that renal disease causes thinning of the blood plasma, hypertrophy of the left ventricle and excessive arterial pressure. If the arterial tension is increased beyond a certain point or the plasma of the blood becomes further thinned, œdema and anæmia of the brain are produced and uræmic symptoms result. There are fatal objections to this theory. These are: 1. That there may be marked cerebral symptoms without arterial tension. 2. That the specific gravity of the serum is often normal in typical uræmia. 3. That there are uræmic patients in whom neither cerebral anæmia nor cerebral œdema are found at autopsy. 4. That a marked degree of anæmia of the brain and of œdema is occasionally found in the absence of all symptoms resembling uræmia.

It is, however, clear from clinical study that there is often a close association between certain uræmic symptoms, especially convulsions

and dyspnœa and high arterial tension. Nor is there any doubt that when we reduce excessive vascular tension by means of vaso-dilators, such as nitro-glycerine, we often relieve the symptoms in the case of dyspnœa, sometimes in a striking degree. At present it appears probable that the high arterial tension of uræmia is due to the action of toxic material in the blood. It is not at all inconsistent with this view that variations in the circulation of the central nervous system should influence, in important ways, symptoms which, like dyspnœa, are of central origin.

Although we cannot accept the theory of Traube as advanced by him, the appearances observed in the central nervous system in persons dying of uræmia[1] (especially the loss of chlorophyllic substance seen in nerve cells) indicate that mechanical conditions, such as local anæmia, congestion or œdema, have been operative in damaging the nerve elements. It seems probable that these conditions are not primary, but depend on toxæmic states.

Another theory of uræmia which cannot be passed by, is that of Brown-Sequard, who holds that the kidney elaborates an internal secretion which is essential to health, and the suppression of which is largely responsible for the phenomena of uræmia ; the accumulation in the blood of toxic substances which should be excreted by the urine having little or no influence on the causation of these phenomena. This conception of uræmia rests mainly on the alleged fact that the injection of kidney extract into the circulation of a nephrectomized dog causes the temporary disappearance of uræmic phenomena. The evidence which has been advanced to establish this fact must be regarded as insufficient. Thus the observation of Brown-Sequard that the injection of kidney extract causes an increase in the muscular power of nephrectomized dogs, rests on a small number of experiments which appear neither to have yielded decided results nor to have been subjected to careful control, and Meyer's contention that the injection of renal extract gives marked relief to the dyspnœa of double nephrectomy likewise rests on a small number of observations that seem distinctly to call for proper controls. Nor can we place much reliance on the claims of Teissier and Frenkel, in a recent publication, that the injection of a few cubic centimeters of renal extract in the human uræmic subject is capable of rendering a hypotoxic urine hypertoxic by stimulating the elimination of toxines through the urine at the same time that the symptoms of uræmia are ameliorated. Consider-

[1] These changes are not by any means distinctive of uræmia, but occur in a variety of conditions. According to Dr. James Ewing they are best seen where the nerve elements have been subjected to pressure, as in cerebral hemorrhage.

able personal experience makes me highly skeptical as to the propriety of our drawing inferences as to the condition of the blood from the effects of intravenous infusions of urine in animals. A very obvious and serious gap in the experiments of Teissier and Frenkel is the absence of observations on the toxic salts ingested with the food and eliminated with the urine, the toxicity of the urine, both in health and disease, being largely dependent on its potassium salts. Future investigations may show that the kidney elaborates an internal secretion, but at present we are justified in taking the position that the observations now relating to this question do not help us in explaining the pathology of uræmia.

Passing now to a consideration of the clinical types of uræmia with a view to the discussion of their pathology, it is desirable first to make reference to the phenomena of double nephrectomy in dogs and their relation to human uræmia of obstructive origin.

The alterations in the composition of the blood that are entailed by double nephrectomy are of the greatest interest in the study of the pathology of uræmia, for they necessarily represent the results of the most extreme degree of renal incompetency *per se* and without complicating factors such as are commonly present in human uræmia. The following description of the symptoms and pathological alterations incidental to experimental uræmia, is based on a series of 10 successful cases in dogs, as well as on cases in the pig and rabbit—and also upon a number of instances in which the ureters were tied upon both sides. It may be stated at the outset that the symptoms were essentially the same in the case of double nephrectomy as in ligation of the ureters. These symptoms consist, in a typical case, of moderate prostration following the operation, of repeated vomiting[1] sometimes associated with diarrhœa, of slow and deep respiration, of slow, full and high tension pulse and, not rarely, of fibrillary twitchings. In only one instance did true convulsive seizures occur. Death is usually preceded by a period of drowsiness or actual coma. In none of my animals was the operation survived more than four and a half days, and most of them lived less than three days. In cases unaccompanied by infection the temperature is generally one or two degrees below normal for one or two days before death.

A considerable number of observations have been made by me to determine whether the blood of nephrectomized dogs is more toxic to rabbits than the blood of normal dogs; or, to put it a little differently,

[1] The vomiting referable to the removal of the kidneys must be distinguishable from that which results from peritonitis accompanying accidental infection in these cases.

to determine whether the experimental uræmia of double nephrectomy is comparable with human uræmia of the convulsive type as regards the toxicity of the blood. There can be little doubt that this is a most important question in the pathology of uræmia, and I regret that it is not possible for me to make an unqualified statement in regard to it. Owing to the crudeness of our methods of studying the toxic properties of the blood, it is not possible to detect moderate deviations from the normal toxicity. It can, therefore, only be said that there does not seem to be a marked difference in the toxic properties of the blood within 48 hours after nephrectomy as compared with the blood of the same animal previous to nephrectomy, but that the toxicity of the blood seems to be increased in dogs that live a longer period.

As regards the changes in the chemical composition of the blood, our information is much more positive. We know, for example, that the urea of the blood is remarkably increased after double nephrectomy —often reaching ten times the normal percentage at the end of three days. The extractives are also distinctly increased. A moderate increase in the total salts of the blood is probably a regular feature of the blood of nephrectomized animals. The potassium salts may be somewhat increased, but on the other hand may not be appreciably changed. The total proteids undergo no alteration in amount. A very interesting feature of the blood has been the marked increase in fibrin which was noted in a number of the nephrectomized dogs. This observation, though one of much interest if confirmed, has not yet been subjected to the controls which are necessary to establish it as a fact, for a very definite source of error remains to be eliminated. This consists in the fact that a part of the increase in fibrin noted after nephrectomy may be due to the bleeding which was practised several days before nephrectomy for the purpose of establishing a basis of comparison before and after operation, for it is known that the fibrin of the blood is increased by bleeding.[1]

In order to be able to compare the symptoms of double nephrectomy with the obstructive type of human uræmia, the cases of

[1] Since this paper was read I have succeeded in several instances in performing double nephrectomies and ureter ligations without losing more than a few c.c. of blood, through hemorrhage. All these animals have shown a doubling of the normal fibrin content of the blood after a few days. A dog subjected to laparotomy without nephrectomy, but with a moderate loss of blood, showed no increase in the fibrin content of the blood.

These observations seem of especial interest in connection with the altered toxicity of the blood after nephrectomy, but other sources of error remain to be eliminated before the increase in fibrin can be positively attributed solely to the suppression of renal functions.

prolonged anuria from obstruction accessible in literature were subjected to analysis. Of the 41 apparently reliable cases in which anuria lasted four days, 35 occurred in males. This striking difference in sexual incidence is probably explained by the nature of the obstruction to the escape of urine. In 14 of the 21 cases in which an autopsy was made the ureter or pelvis of the kidney was obstructed by a calculus, on one or both sides, the obstruction thus created being the cause of the anuria. I have been unable to find the record of a case in which anuria in a female was due to obstruction of the ureter or pelvis by a calculus. Of 36 cases in which there was either absolute anuria (if we can trust the histories) or in which only an insignificant quantity of urine was passed, the condition in 11 cases lasted more than 4 days and less than 7, in 18 cases lasted from 7 to 14 days, and in 7 cases lasted longer than 14 days.

Although the records are not wholly satisfactory, they serve to bring out clearly some important facts regarding the symptoms of obstructive uræmia. It is interesting to note that in seven of our forty-one cases it is definitely stated that no uræmic symptoms occurred, although some of the cases were of considerable duration (5, 5, 6, 7, 8, 9 and 11 days). Although it is not unlikely that some of the unobtrusive indications of uræmia were overlooked in these cases, it is fair to suppose that there were no well-marked uræmic symptoms. It seems clear that it is the rule for uræmic symptoms not to begin for several days after the commencement of the anuria. In a number of cases more than a week elapsed before pronounced indications of uræmia began. In twelve of the forty-one cases it is noted that vomiting was present at some period of the anuria. In one case (that of Russell, lasting twenty days) it is said that vomiting was present from the beginning. Diarrhœa does not appear to be so frequent a symptom as vomiting. It was noted in only six cases. Headache was described in only six cases. Insomnia, with restlessness, was observed in several instances, and may be present from the beginning. Muscular paralysis was not recorded in any of the cases, although a considerable degree of muscular prostration was repeatedly observed, and is probably a relatively early symptom in most instances. Pronounced delirium was a rare symptom. General convulsions is another uncommon symptom, having been noted in only five of the forty-one cases. Twitchings of the muscles, not sufficiently wide in range to constitute convulsions, were observed in eleven cases. According to Roberts this is a highly characteristic symptom of obstructive anuria. As regards the state of the mental faculties it seems safe to say that death is usually preceded by drowsiness, if life lasts more than

a week, but that the patient may in most instances be roused at any time.

In four cases a urinous odor of the breath was noticeable and in one of these the skin also had a urinous odor. In one instance the breath is described as having an ammoniacal character. In one patient, not included in the collection, the suppression lasted four days and the skin of the neck and face was covered by crystals of urea. An important clinical feature of obstructive uræmia is that the temperature is seldom elevated. In only one case is there a record of any fever, and in this the rise was slight. It is clearly the rule for the temperature to remain normal throughout or to be a little subnormal during the last days of life.

On comparing the symptoms of these two sets of cases, the human obstructive uræmia and the experimental uræmia following double nephrectomy or bilateral ligation of the ureters, several important resemblances become apparent. Thus vomiting is an early and frequent symptom, while diarrhœa, though not rare, is distinctively less common. In both groups of cases marked muscular prostration is usual from the beginning. Occasionally, however, there is early restlessness. Indications of delirium are absent in the experimental as in the human cases and paralyses have not been observed. In the terminal stage, fibrillary tremors are common in both the human and the canine cases, while general convulsions are exceptional. Terminal coma may occur in either group, but consciousness can usually be aroused at any time. An important clinical resemblance lies in the fact that the temperature is either normal throughout or slightly subnormal. There are, however, some points of difference. Thus, a patient with both ureters obstructed may live more than two weeks, while a dog with both ureters tied or with both kidneys extirpated lives less than one week. We can hardly attribute this difference in the duration of life to the shock of operation. It may depend on the activity of the skin in man. The ammoniacal breath of human patients depends doubtless on the decomposition of urea in the gastro-enteric tract and the odor of the skin arises from the decomposition of urea in the sweat. It may happen that a greater accumulation of urea occurs in the blood in man than in the dog, owing to his longer survival, and that this occasions the excretion of urea by the gut in the case of man. Notwithstanding these clinical differences, it seems probable that the pathological conditions which are responsible for the symptoms in nephrectomized dogs are essentially those that are responsible for the symptoms of obstructive uræmia—namely, the accumulation in the blood of urea, extractives, inorganic salts, and

perhaps of a toxic proteid material the nature of which is at present unknown.

Coming now to the consideration of other types of human uræmia, we find ourselves upon uncertain ground when we try to bring the various clinical phenomena into relation with the pathological state or states which constitute their basis. This is because the pathological knowledge which we possess is still exceedingly meagre and probably inadequate to form the basis of a permanent pathological classification of the different combinations of systems which we call uræmic. There are, however, certain facts, some of which have already been alluded to, that seem to me to help us in the interpretation of the phenomena of human uræmia, and to these I wish to direct your attention.

There is a well recognized group of patients with chronic nephritis whose leading characteristics clinically are high arterial tension, dyspnœa and slight albuminuria, and sometimes headache. Although the kidneys of such patients present considerable variations in their gross character, there is in all cases widespread degeneration of the secreting tubules, fibrous changes in the tufts, and a distinct increase in the intertubular connective tissue. Cases of this character are often benefited by venesection (at least temporarily) and it has thus become possible to obtain the blood for study in a number of instances. As already stated, it is not possible to say whether or not the serum from such patients is regularly more toxic than normal, although it appears as if this were the case in some instances at least. It is usual in these cases for the blood to contain an increased percentage of urea, thus affording a positive indication that the kidney is not wholly competent to perform its excretory functions. Cases of nephritis of this type may be the distant consequences of infection, but there is no reason to think that pathogenic bacterial products are present in the blood at the period when these cases run a chronic and entirely afebrile course. The only obvious pathological condition of the blood that is likely to be connected with the characteristic exacerbations of dyspnœa and the increase in arterial tension, is the retention in the blood of constituents that should be excreted, perhaps including an unknown toxic proteid material. In other words (leaving aside the fact that the water of the plasma may be increased in such cases) the condition of the blood in the cases described is probably analagous to the condition which was described as characteristic of double nephrectomy, and which, in all likelihood, is the basis of human obstructive uræmia. At least this much is certain—in the three different conditions which we have considered, double nephrectomy, obstructive uræmia and chronic nephritis, with high tension and uræmic dyspnœa—there is an

actual retention of urea in the blood and not improbably an increased toxicity of the blood due to a proteid constituent. It is, of course, obvious that there are clinical differences between human obstructive uræmia and the dyspnœic type which this pathological conception does not explain. We must, however, remember that in the one case we have to do with an acute condition arising sometimes in persons whose vascular system is not markedly altered, while in the second case the toxæmia is a chronic state arising in a person who, simultaneously, and for reasons not understood, has developed cardio-vascular fibrosis. It is possible that this cardio-vascular fibrosis plays a mechanical part in the production of dyspnœa in the presence of a uræmic toxæmia like that referred to.

In the course of the arterio-sclerotic type of chronic nephritis, with uræmic dyspnœa, etc., as well as in other types of nephritis, gastro-enteric disturbances, especially nausea, vomiting, and diarrhœa of an intractable character, are occasionally observed. It will be remembered that vomiting and diarrhœa are features of experimental uræmia from nephrectomy and of obstructive uræmia.

There can be no doubt that these symptoms are due to a retention uræmia in which urea, extractives, etc., accumulate in the blood in large excess and are finally excreted by the gastro-enteric mucous membrane, causing diarrhœa, and in which vomiting is caused by the action of these toxic substances upon the medulla. I cannot undertake to say whether the known retained constituents of the blood (urea, extractives, salts) are in themselves responsible for these symptoms or whether unknown substances contribute to determine these symptoms. There are several facts which are of significance in this connection. One is that the injection of urea into the blood eventually causes diarrhœal discharges containing urea. Another fact is that in every case of uræmia that I have studied in which uræmic vomiting or diarrhœa has been a feature, the blood has contained a marked excess of urea, etc. Again we find that vomiting and diarrhœa are characteristic symptoms both of obstructive uræmia and of double nephrectomy. We know that in the former cases crystals of urea may be found on the skin and that in the latter urea may be found in the intestine. Considering these facts together we cannot but feel justified in believing that the known retained constituents of the blood play a part in the production of the digestive symptoms of uræmia, possibly a leading part.

In the course of a small proportion of cases of nephritis, convulsions constitute an obtrusive occurrence. The convulsive seizures may form part of the history of almost any type of nephritis—of nephritis

with preponderant parenchymatous change to nephritis with extreme connective tissue alterations. In a certain number of cases the symptoms previous to the convulsive seizures have been those of the type already referred to, with high tension pulse, dyspnœa, moderate albuminuria, etc. In other words, this type of uræmia is liable at any time to become modified by spastic phenomena. It should be noted that in some of these cases, where convulsions are thus superposed, the temperature remains normal until the seizure, and is then only slightly elevated—not more than we might expect from violent muscular action. How do these cases differ pathologically from the high tension type of uræmia without convulsive seizures ? At the beginning of this paper reference was made to the fact that the toxicity of the blood was found to be markedly increased in many of eighteen cases of convulsive uræmia and at least apparently increased in all. It was found that the toxic properties of the serum in this group of cases were more pronounced than in the non-convulsive group with high tension. Moreover, it was found that in some of these convulsive cases the urea was not increased beyond the normal percentage. In a very few instances the urea, the extractives and the potassium salts were apparently within normal limits. It is plain that if the convulsions in these cases are of toxæmic origin they must depend upon some other substance than urea, and it is not unlikely that they depend on the presence of the proteid substance to which the exaggerated toxicity of the blood appears to be due. There does not, however, appear to be any significant difference between the convulsive and the non-convulsive group of cases, the difference in the toxicity of the blood being probably one of degree rather than of kind. Again, the clinical facts lend support to the view that the pathological basis of the two sets of cases cannot be very different, for the spastic phenomena are often so slight as to constitute only fibrillary twitchings that recur infrequently and bring about no noticeable change in the condition of the patient. It may be that the presence or absence of these nervous phenomena is connected with slight variations in the degree of toxæmia or with temporary alterations in the circulation of the brain.

The evidence thus seems to favour the view that in the group of cases which has been discussed, the symptoms are dependent largely upon renal insufficiency and upon alterations in the blood that are secondary to this condition. It is important to realize that although a kidney may be competent to excrete urea so actively as to prevent the accumulation of urea in the blood, it does not necessarily follow that it is competent to excrete, or to transform and excrete other sub-

stances which a healthy kidney would not permit to remain in the blood.[1]

It may be that further studies will show that the essential pathological element in the forms of uræmia already considered is the presence of the proteid serum poison to which reference has been made; although in the form of uræmia characterized by gastro-enteric derangements, the accumulation of urea, salts, etc., appears to be a regular and probably a determining factor.

An element quite different from simple renal insufficiency enters into many cases of uræmia, namely that of infection.

There is a small but suggestive group of patients who, after exposure to cold or wet, develop high fever, partial suppression of urine, albuminuria and perhaps hæmaturia, with headache, delirium and coma. The peculiarity of these cases is that the kidneys have previously been normal so far as can be determined by clinical methods. There seems little doubt that the cerebral symptoms in such cases of acute degeneration of the kidney or acute exudative nephritis are due wholly to the action of toxines and not to the retention of substances in the blood which are normally eliminated by the kidney.

These unusual but instructive cases appear to me to represent the type of uræmia most widely removed from human obstructive uræmia in its pathological basis. As might be expected, these cases retain their purely infective type only a short time, for the damage to the kidney soon leads to pronounced insufficiency and to the accumulation of urea, extractives, etc., in the blood in marked excess. A condition analogous to that just described can be produced in monkeys by the subcutaneous injection of pathogenic bacterial filtrates.

In a considerable number of cases of chronic nephritis which have run an afebrile course there is a sudden development of fever, partial suppression with increase in the albumen of the urine and cerebral symptoms such as delirium, coma or convulsions. At autopsy the kidney may show the lesions of an acute nephritis grafted upon those of a chronic nephritis. Post-mortem cultures made from the blood and various organs frequently show the presence of pyogenic or other pathogenic bacteria. In short we have in these cases both clinical and pathological evidence of the occurrence of an acute infection. It seems reasonable to suppose that many of the symptoms which we call uræmic in these terminal cases are due to the combination of this infection with a pre-existing toxæmia due to chronic renal insuffi-

[1] The increase in the fibrin content of the blood which I have found in some cases of this sort is of interest in this connection, though its significance is still uncertain.

ciency. But such infections are by no means always terminal states. It has been shown by Welch and others that patients with chronic nephritis are especially susceptible to infection, and it often happens that a patient with chronic diffuse nephritis develops grave cerebral symptoms at the time of a trivial infection which causes a tonsilitis, a slight bronchitis or an otitis,—symptoms which we very properly look upon as uræmic, but from which there is apparently complete recovery.

Reference has already been made to the fact that the urea content of the blood was found to be almost regularly increased in persons dying of acute lobar pneumonia, in other words, that renal insufficiency for urea is a characteristic of fatal pneumonias. This observation suggests the question whether we are to regard a markedly excessive accumulation of urea in the blood as an indication of uræmia even in the absence of typical clinical indications of uræmia. I strongly incline to the view that we should extend our conception of the term uræmia to include every case of renal insufficiency for urea although well defined uræmic symptoms be wanting. It has been made clear that typical uræmic symptoms may arise in persons whose blood shows no increase in urea, but this fact does not deprive the accumulation of urea, salts, etc., of clinical significance ; it merely illustrates that the pathological basis of what is clinically termed uræmia is not always the same. It seems to me desirable that we should regard any toxæmia as uræmic which can be shown to depend on the incapacity of the kidney to perform the functions of a healthy kidney, whether these functions consist simply in the elimination of substances as they exist in the blood furnished by the renal artery, or whether they shall be shown also to consist in the transformation of certain elements of the blood previous to elimination.

Again it is only rational that we should recognize that the essential elements of a uræmic intoxication may exist without being present in such a degree as to cause obtrusive and typical uræmic symptoms. Or, to restate the fact in a different form, *we should recognize that there is such a thing as a latent uræmic intoxication.* Such a latent uræmia is probably present in many forms of disease, especially acute disease, such as pneumonia, where the kidney is the seat of lesions, aud in chronic nephritis. In the former condition it constitutes a complicating state.

The fact that such a toxæmia may be masked by associated conditions or may be in itself unrecognizable clinically does not prove that it is a state which exerts no influence in determining prognosis.

In conclusion a word must be said about the most obscure type of

uræmia—puerperal eclampsia. Efforts have been made to connect this state with the formation of toxic products formed by the chemical activities of the living cells of the embryo, with the absorption of toxic material formed in the intestine and with the accumulation of urea in the blood as the result of nephritis or of pressure on the renal vessels, but the efficacy of these supposed agencies still remains unproved.

My personal experience with puerperal eclampsia is limited to the study of the blood of six victims of this state.[1] In at least three of these cases the urea of the blood was not increased in percentage. It seems highly probable that the toxicity of the blood was distinctly increased in at least two of these cases. Of the other cases it cannot be positively stated that the blood was more toxic to animals than is ever the case with the blood of non-eclamptic puerperal women, nor, on the other hand, can it be stated that the blood was not more toxic than normal.

At the present time there is a controversy as to the toxicity of the blood of eclamptic women, which can be definitely settled only by numerous and very carefully conducted observations. Although there is thus considerable uncertainty as to whether an increased toxicity of the blood is an essential feature of puerperal eclampsia there is important indirect evidence of the existence of such a toxæmia. This consists in the presence of anæmic and hemorrhagic areas of necrosis in the livers of women dying of eclampsia.[2]

Schmorl, who first described these striking lesions, regards the thromboses of the capillaries and small periportal veins with which they are associated as dependent on the passage into the blood of placental elements and products of placental degeneration.

Flexner has succeeded in producing similar alterations in the liver by means of experimental intoxications, and there can be little doubt that we must regard the necrotic changes in the organs of eclamptic women as dependent on a toxæmia. How this toxæmia arises and how it is related to the toxæmias of nephritis already discussed remains to be discovered.

Although this sketch of the pathology of uræmic conditions, made from a somewhat personal standpoint, shows us to be in possession of a meagre fund of knowledge respecting the pathological basis of uræmia, we may confidently hope for further enlightenment from experimental pathology. It seems to me that future researches should have refer-

[1] The blood from these patients was obtained through the courtesy of the attending physicians of the Lying-in Hospital of New York.

[2] I have never met with these lesions in the livers of persons dying from other forms of uræmia than puerperal eclampsia.

ence especially to the following topics: The toxic properties of the blood of uræmic patients, the physiological and chemical changes induced in the blood by nephrectomy, and the influence of intoxications of intestinal origin upon the normal organism and upon organisms which are the seat of nephritis. That the state of bacterial activity in the intestine is capable of exerting an important influence upon uræmic conditions is suggested by the observation which I have made that the albuminuria of a dog with chronic nephritis can be strikingly increased by feeding with cultures from the stools of entero-colitis It is also suggested by the exacerbation of symptoms which we sometimes observe clinically in human patients after gross errors in diet.[1] This relation deserves further attention, as it is of the utmost practical importance in chronic uræmias.

I had hoped to refer this evening to methods of treatment in uræmia, but am conscious of having already overstepped the limit of time imposed by reasonable usage.

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[1] Nephritis and uræmia may also arise in children as a consequence of intense entero-colitis.